Travel or Deployment
Diarrhea

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Lecture Objectives

- Definitions
- Scope of disease and Epidemiology
- Acute Diarrhea
  - Pathogens involved
- Chronic Diarrhea
  - Pathogens involved
- Diagnosis
- Treatment
- Prevention

Diarrhea Deaths

- **Second only to cardiovascular disease as a cause of death worldwide**
  - **Leading cause of childhood death**
  - **5-6 million children die annually in Asia, Africa and Latin America**
  - **~10,000 children die annually in the US**
  - **Averages of 7-19 cases per child per year in some areas**
- **Deaths in adult travelers with diarrhea are rare**

Pediatric Deaths due to Diarrhea

Table 5. Global estimates of the annual number of diarrhea and rotavirus deaths among children <5 years of age, by income group

Income group	Total no. (x1,000)		Diarrhea deaths		Rotavirus deaths[b]		Risk of dying from rotavirus by age 5
	Births	Deaths	Median % (IQR[a]) of total deaths	Median no. (IQR) of deaths (x1,000)	Median % (IQR) of diarrhea hospitalizations	Median no. (IQR) of deaths (x1,000)	
Low	70,447	8,595	21 (17–30)	1,805 (1,461–2,579)	20 (16–27)	361 (289–487)	1 in 205
Low middle	37,402	1,609	17 (11–23)	274 (177–370)	25 (20–33)	69 (55–90)	1 in 542
Upper middle	11,520	366	9 (5–17)	33 (18–62)	31 (25–42)	10 (8–14)	1 in 1,152
High	9,931	60	1	<1	34 (28–38)	<1	1 in 48,680
Total	129,300	10,630	NA	2,112 (1,657–3,012)	NA	440 (352–592)	1 in 293

Parashar et al; Global Illness and Deaths Caused by Rotavirus Disease in Children EmergInfDis; 9 (5):165-172, 2003

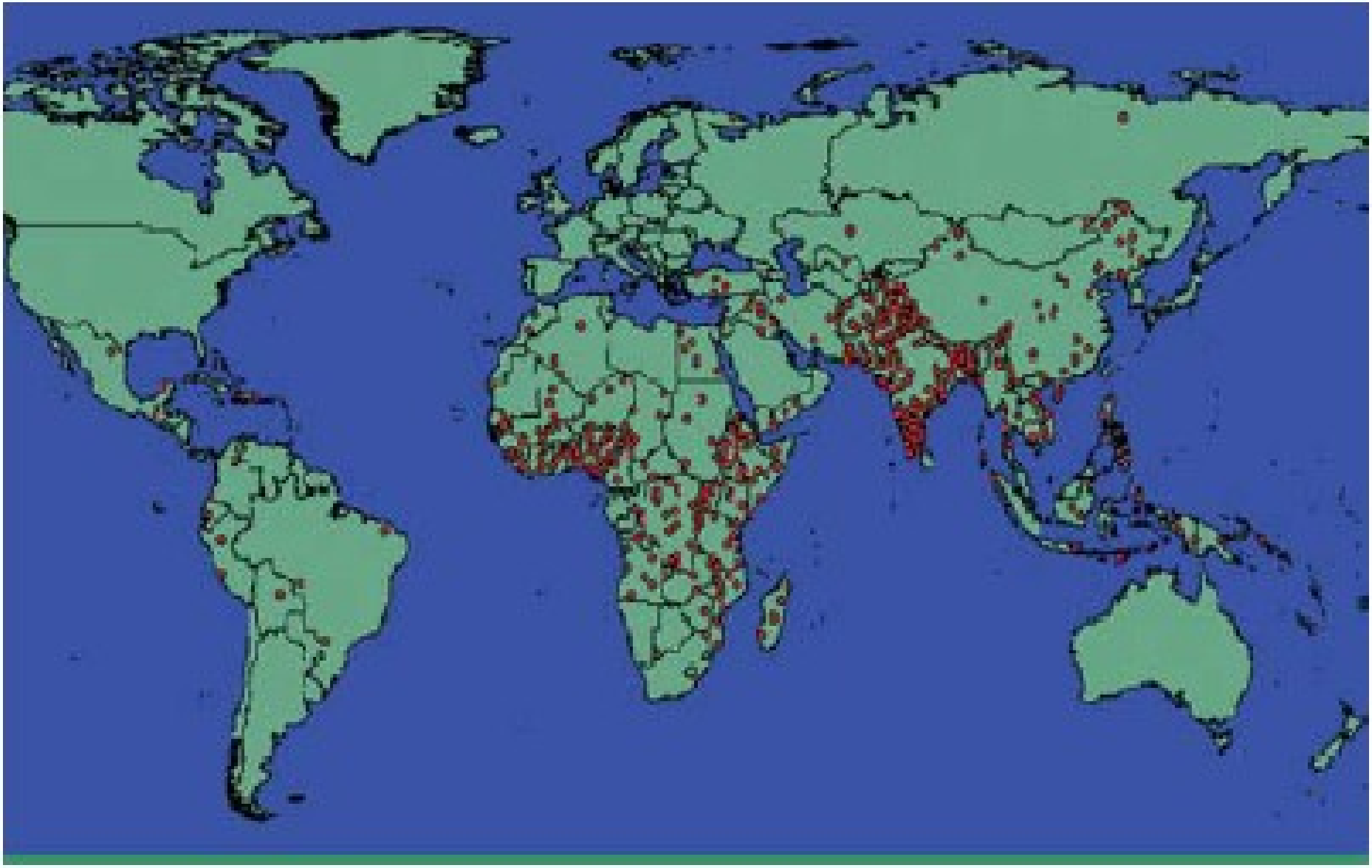


Figure 2. Estimated global distribution of 440,000 annual deaths in children caused by rotavirus diarrhea. One dot=1,000 deaths

Diarrhea in Travelers and Deployments

HORTUS SICCUS
REGIME de TERREUR
PROJETS AVORTES
French Generals retiring on account of their health: – with Lepaux presiding in the Directorial Dispensary

Diagnoses among ill travelers returning from the developing world

Diagnosis	All Regions (N=17,353)	Caribbean (N=1115)	Central America (N=1326)	South America (N=1675)	Sub-Saharan Africa (N=4524)	South Central Asia (N=2403)	Southeast Asia (N=2793)	Other or Multiple Regions (N=3517)†
				number of cases per 1000 patients				
Systemic febrile illness‡	226	166	153	143	371	171	248	145
Acute diarrhea‡	222	196	234	219	167	327	210	238
Dermatologic disorder‡	170	261	225	264	127	130	212	125
Chronic diarrhea‡	113	132	173	130	57	129	97	149
Nondiarrheal gastrointestinal disorder‡	82	87	75	82	70	74	58	121
Respiratory disorder‡	77	45	49	50	77	89	97	86
Nonspecific symptoms or signs‡	70	53	51	59	75	85	63	77
Genitourinary disorder‡	35	29	11	27	51	25	29	40
Asymptomatic parasitic infection‡	30	15	26	33	29	44	30	24
Underlying chronic disease‡	19	14	23	18	20	14	13	27
Injury‡	14	23	11	14	7	15	14	21
Neurologic disorder‡	15	23	24	16	10	15	10	16
Adverse drug or vaccine reaction‡	12	4	5	5	26	12	8	8
Psychological disorder‡	12	8	20	15	8	12	10	18
Tissue parasite‡	10	5	5	11	22	4	3	7
Cardiovascular disorder	8	12	7	5	8	7	5	10
Obstetrical or gynecologic disorder	3	3	2	2	4	3	3	3
Ophthalmologic disorder	2	2	2	2	2	1	1	2
Dental problem	1	1	1	1	1	0	2	1
Death	1	1	0	0	1	3	0	1
Loss to follow-up‡	8	9	12	9	8	5	4	13

Freedman et al. N Engl J Med 2006;354:119-3

Traveler's Diarrhea
Prevention and Self Management

- **The risk of traveler's diarrhea for each week spent in a developing nation is 20 - 25%.**
  - **Varies from country to country, and in different areas in one country.**
  - **Rates of 40 - 60% are not uncommon with several weeks travel.**
- **Mortality has not been described.**
- **Morbidity may be significant.**
  - **Untreated cases last an average 3 - 4 days.**
  - **Affected persons average 17 unformed stools.**
  - **Cramps, nausea, vomiting, and fever may be present.**

Traveler's Diarrhea
Definitions

- **Healthy person < 150 mL (of liquid in) stool in one or more BMs per 24 h**
- **A patient with diarrhea often passes > 200 mL of liquid in stool in > 3 unformed movements in 24 h.**
- **If < 150 mL total liquid volume, generally considered "loose stools" and not diarrhea**
- **Traveler's Diarrhea is defined as ≥ 3 unformed stools passed in 24 h and at least one associated symptom of enteric dz:**
  - **nausea**
  - **vomiting**
  - **abdominal pain**
  - **fever**

Traveler's Diarrhea
Associated Risks

- **Rural areas and tropical climates associated with > risk than cooler climates and urban areas.**
- **The major source of infection appears to be food.**

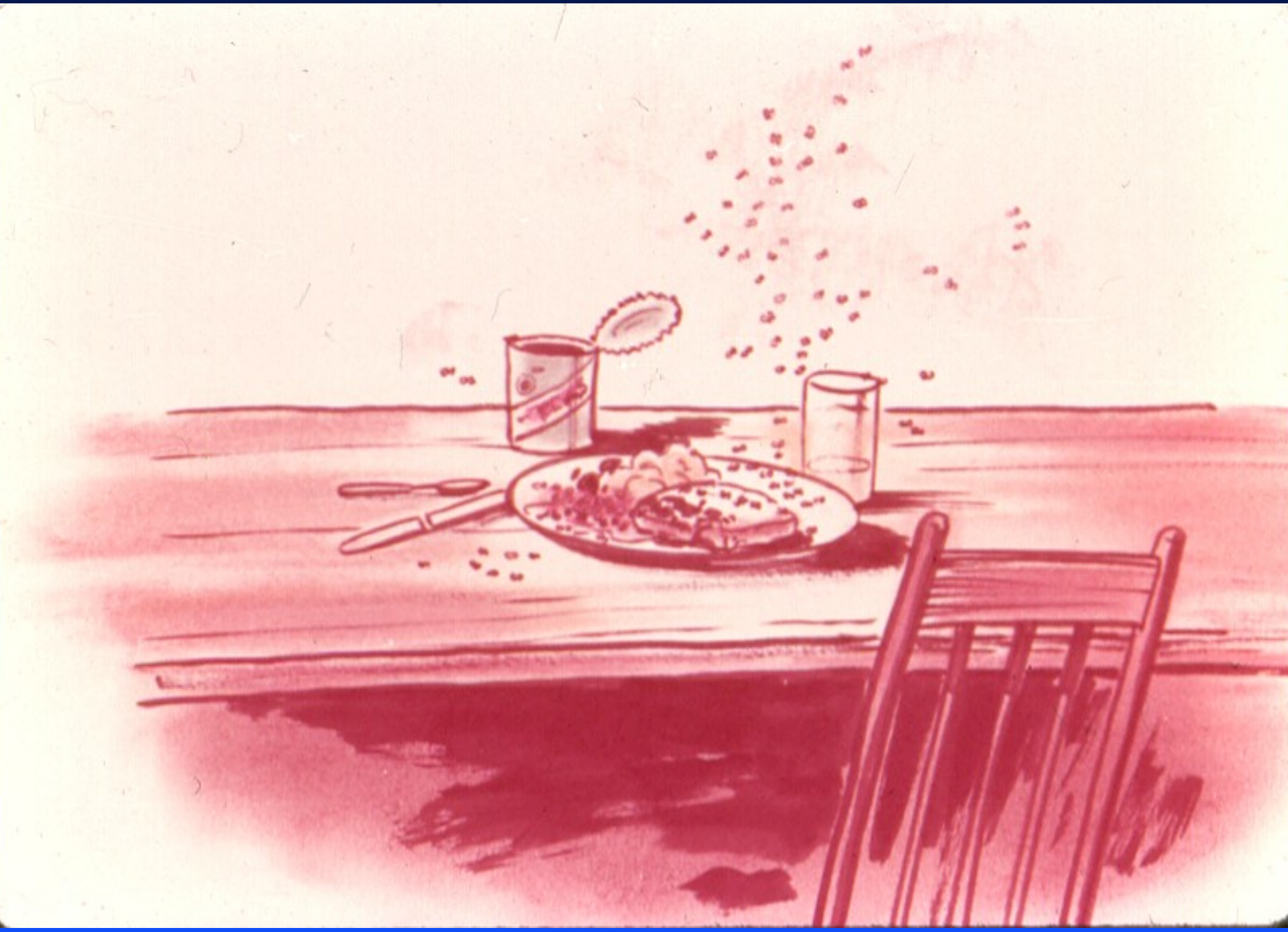
  Food cultures may reveal bacterial contamination equivalent to feces.
- **Water-associated diarrhea typically caused by viruses or parasites > bacteria.**
  - **Freezing decreases, but does not eliminate, bacteria in water.**
  - **Heating to boiling for one minute destroys most pathogens.**
  - **Boiling for five minutes is recommended to kill all pathogens.**

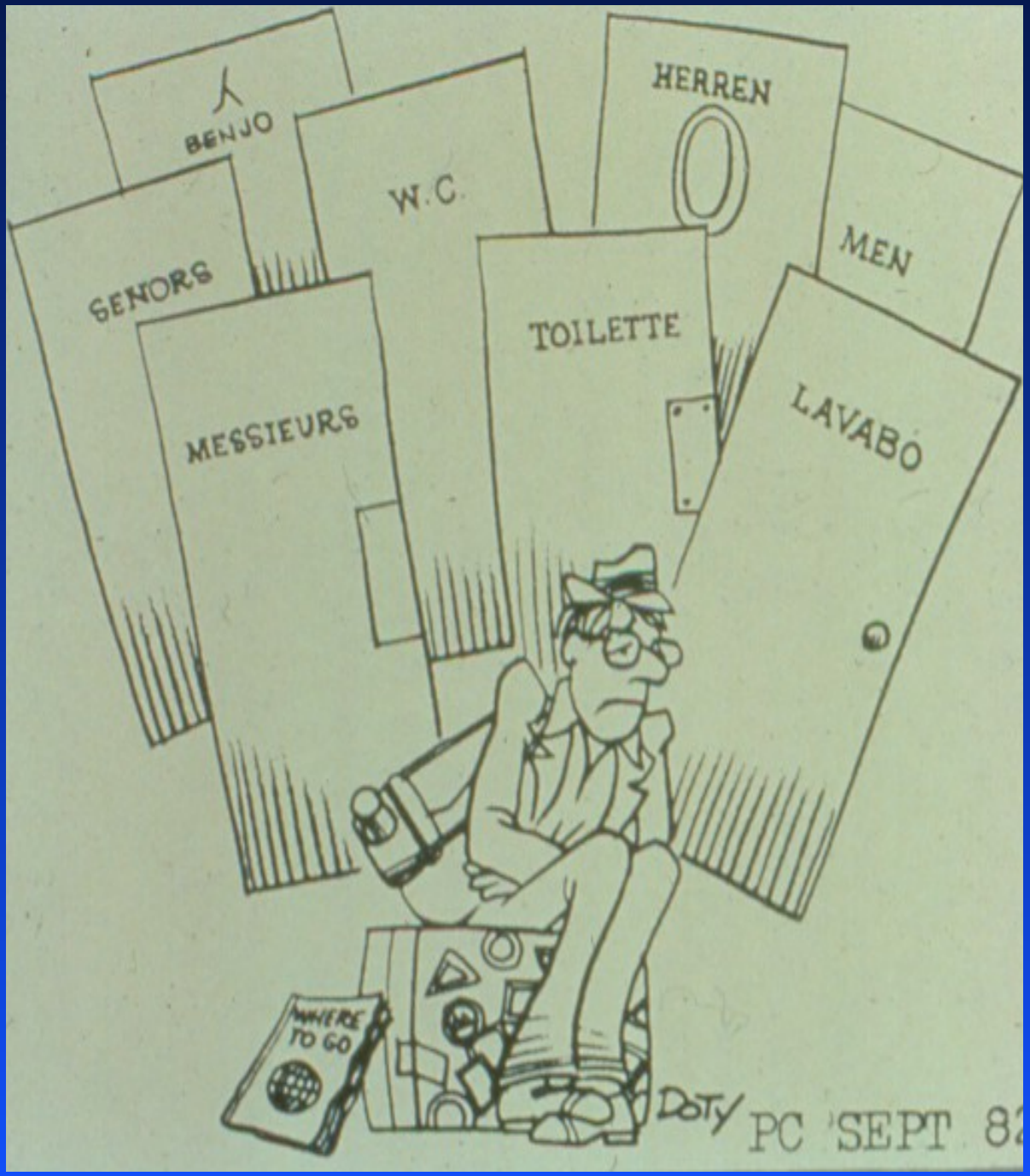
Are you eating food or feces?

- **Fecal contamination determined by presence of *E.coli* in food from Guadalajara:**
  - **28 hot sauces from 12 restaurants**
  - **67 - 100% of the different sauces were contaminated**
  - **mean number of colony counts: 3,100 - 13,500 colonies/gram (some with 30,000)**
- ***E. coli* contamination in Mexican restaurants in Houston:**

  40% of 25 sauces contaminated with a mean of 3.6 colonies per gram.

DuPont et al Abstract 204 at 36th IDSA in *CID* Vol 27 No 4: Oct98




BENJO
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MEN
LAVABO
WHERE TO GO
DOTY
PC SEPT 8

DIDN'T WASH HANDS
MEN

Common Pathogens Causing Diarrhea in Travelers to Mexico

	Organism	Percent
Bacterial	***Enterotoxigenic E. coli***	**40**
	Shigella spp.	**15**
	Salmonella spp.	**7**
	Enteroadherent E. coli	**7**
	Enteroinvasive E. coli	**< 5**
	Campylobacter jejuni	**< 5**
Viral	***Rotavirus***	**5-10**
	Norwalk virus	**5-10**
Parasitic	***Giardia lamblia***	**2**
	Entamoeba histolytica	**1**
	Cryptosporidium	**<1**
Unknown		**<5**

Ericsson and Johnson in Travel Medicine Advisor 2003

Escherichia coli

Serologically Defined

- **O serogroup (lipopolysacharide)**
  - **> 171 O serogroups**
- **H serogroup (flagellar Ag)**
  - **> 70 H serogroups**
- **K serogroup (capsular Ag)**

ETEC
Enterotoxigenic E. coli

- **Most common worldwide cause of Traveler's Diarrhea**
- **Source: "Fecalized" food >> water.**
  - **Need 10^8 to 10^{10} organisms to cause dz.**
- **Incubation: 24 - 72 hours**
- **Clinical: Profuse water diarrhea, nausea, cramps, low-grade fever x 3 - 5 days**
- **Labs: Fecal leukocytes, blood, and mucous are NOT present.**
- **Rx: Fluoroquinolones and rifaximin**
- **Pathogenesis: Heat labile (LT) and stable (ST) toxin produced.**
  - **LT toxin is molecularly similar to the cholera toxin.**

EHEC

The strain that made *E. coli* a household name

- Not a frequent cause of traveler's diarrhea
- O157:H7 assoc with most US cases of hemolytic uremic syndrome
- Source: undercooked ground meat, salami, milk, others. O157:H7 is frequently found in stool of cattle.
  - 1982 multi-state outbreak associated with hamburgers; institutional outbreaks
- Incubation: 24 - 72 hours
  - very infectious, 10-100 organisms
- Clinical: Bloody diarrhea and abdominal pain without fever
  - no mucosal inflammation on bx
  - Up to 5% may develop HUS
- Labs: Stools with RBCs but no fecal leukocytes
  - NOT on most routine screens. Sorbitol MacConkey plates should be used for all bloody diarrhea
- Rx: Antibiotics may increase morbidity and mortality (15-20x > HUS).
- Pathogenesis: Cytotoxin produced resembles Shiga toxin of *Shigella*

E. coli Diarrhea
Other Strains

- **EIEC - *Enteroinvasive E. coli*:**
  - **Incubation: as short as 10 - 18 hours.**
  - **Clinical: indistinguishable from *Shigella* with severe abdominal cramping, watery diarrhea, tenesmus, and fever progressing to scanty stools with blood and mucous**
  - **Pathogenesis: produces Shiga-like toxins**
- **EaggEC - *Enteroaggregative E. coli*:**
  - **mainly infant diarrhea among indigenous population**
  - **increasingly recognized as a cause of traveler's diarrhea, often with resistant strains**
  - **May cause chronic diarrhea in children and HIV infected**
- **EPEC - *Enteropathogenic E. coli*:**
  - **first described category of *E. coli* diarrhea**
  - **almost exclusively in infants, esp developing countries.**

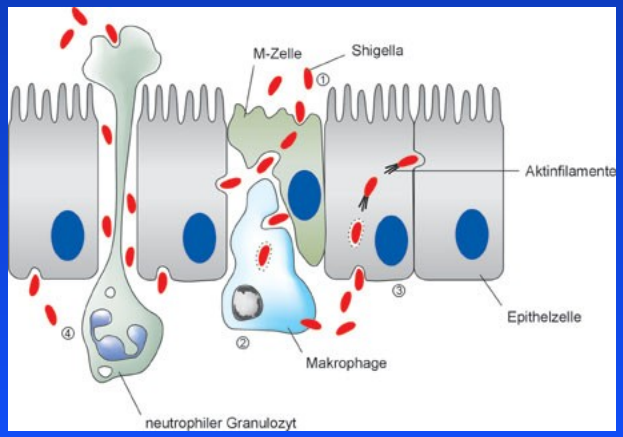
Shigellosis

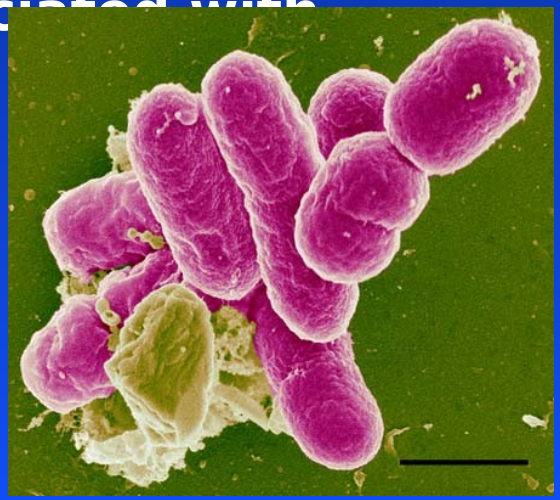
Shigella spp

- **Four species associated with human disease**
  - ***S. sonnei*, *S. boydii*, *S. flexneri*, and *S. dysenteriae***
  - **All but *S. flexneri* are toxin mediated**

- **Source: Fecal-Oral. Food, water and person to person**

- **Incubation: 1 to 7 days (avg 3)**
  - **Ingestion of 10-100 organisms associated with disease**





Shigellosis
Shigella spp

- **Clinical**: Diarrhea, fever, tenesmus, blood & mucous (vomiting in ⅓)
  - Typically biphasic:
    - Begins as frequent, high-volume, watery stools like *ETEC*
    - Gradually lower volume, bloody, mucoid stools as colon involved
- **Labs:** fecal leuks and RBCs common, easily cultured
- **Rx**: quinolones, azithromycin
- **Pathogenesis:** Usually noninvasive but assoc with diffuse colitis
  - Penetration of intestinal mucosal epithelium; but no further extension

Salmonellosis

Salmonella spp

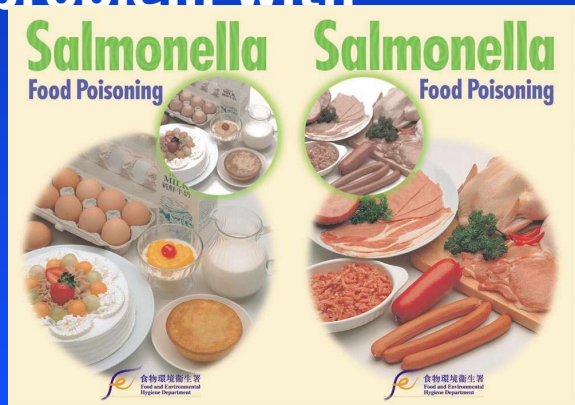
Color-enhanced scanning electron micrograph showing *Salmonella typhimurium* (red) invading cultured human cells

- ***Salmonella*, one species with > 2000 serovars**
  - **thousands of serovars associated with gastroenteritis**
  - ***S. typhi* causes typhoid fever, other serovars cause nontyphoidal salmonellosis**
- **Source: eggs, poultry, meats and milk all can be contaminated**
  - **Developing world more often assoc with contact with infected human**
- **Incubation: variable and related to inoculum size (as few as 10 orgs)**
  - **as short as 6 hours, usually 12 - 36 hours, may be as long as 10 d.**

Salmonellosis

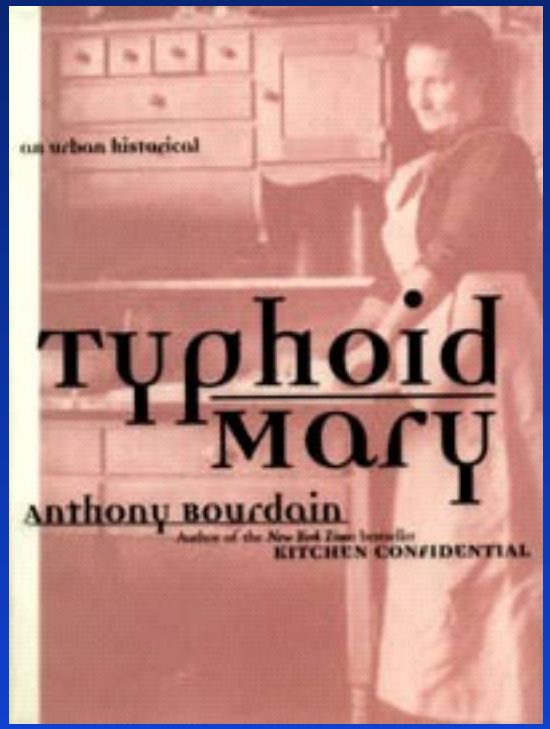
Salmonella spp

- **Clinical:** very varied among individuals, even for same strain.
  - No sx, constipated, watery diarrhea, bloody diarrhea, FUO
- **Labs:** Fecal WBS and RBCs, often invasive and diagnosed by blood cx
  - Bacteria shed for variable period of time, a few weeks to months or years. May be prolonged with treatment.
- **Rx:** not indicated in mild cases, quinolones and 3rd generation cephalosporins. Increasing problem with multidrug resistance.
- **Pathogenesis:** adherence and invasion



Typhoid
Salmonella typhi or *paratyphi*

- **< 500 cases/year in US, most from OCONUS**
- **estimated attack rate for travelers: 1 in 30,000**
- **Source: Transmitted by fecal or urinary contamination of food or water or hand to hand**
  - **Shellfish, milk products, hand carriage, filth flies often implicated sources**
- **Incubation varies with inoculum (3-60 days), typically 1-3 weeks**



Typhoid
Clinical Disease

- **Systemic illness with sudden onset**
  - **sustained fever, HA, malaise, anorexia**
  - **splenomegaly, lymphadenopathy**
  - **truncal erythematous rash “rose spots” (fleeting)**
  - **nonproductive cough**
  - **Constipation in 30%**
  - **Diarrhea eventually develops in ~50%**
  - **Arthralgias and myalgias**
  - **Abdominal pain, delirium and coma in some cases**
  - **Prior immunization does NOT prevent all cases**

- **Case fatality rate of approximately 15% of untreated**
  - **Often related to intestinal perforation**

- **Chronic carriers may occur even after asx dz, especially associated with gallstones and *Schistosomia hematobium***

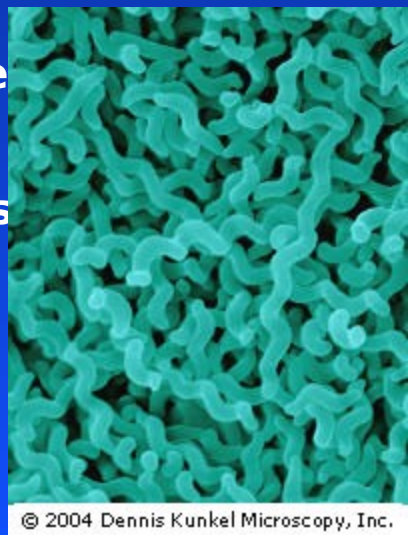
Typhoid

- **Labs: stool cultures are positive in ~30% of cases but often are negative by the time of symptoms**
  - **Blood cultures + in 40-80%**
  - **Bone marrow cultures highest dx yield (up to 98%)**
  - **Anemia and leukopenia are common**
  - **Elevated liver associated enzymes may resemble hepatitis**
  - **Serologic assays less reliable**

- **Rx: quinolones and azithromycin po in mild cases**
  - **3rd generation cephalosporins**

Campylobacteriosis
Campylobacter jejuni

- **Predominant cause of Traveler's Diarrhea n SE Asia > *ETEC***
  - **in North Africa and Mexico more common in winter/dry season**
- **Source: Poultry, dairy products, or unchlorinated water.**
  - **Exposure to a variety of live animals may also be a source.**
- **Incubation: 3 - 5 days, range 1 - 10 days.**
  - **Infective dose as little as 500 organisms**
- **Clinical: 2 - 5 day illness, typically over in 10 days but occasionally prolonged, lasting for weeks**
  - **Fever, abdominal pain, nausea, vomiting, diarrhe bloody)**
  - **Untreated typically shed organisms for 2 - 7 weeks**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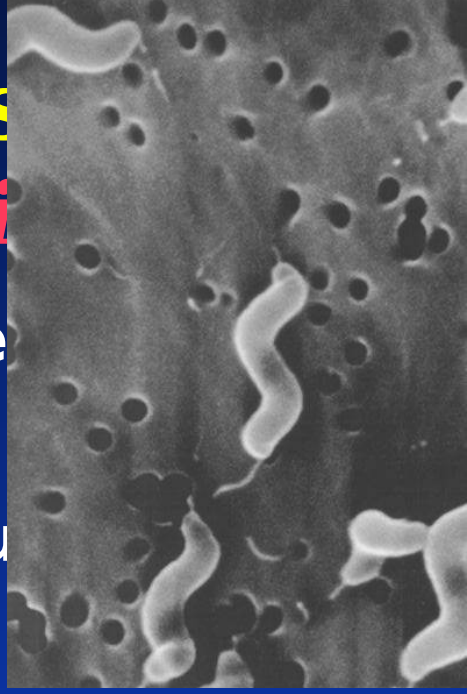
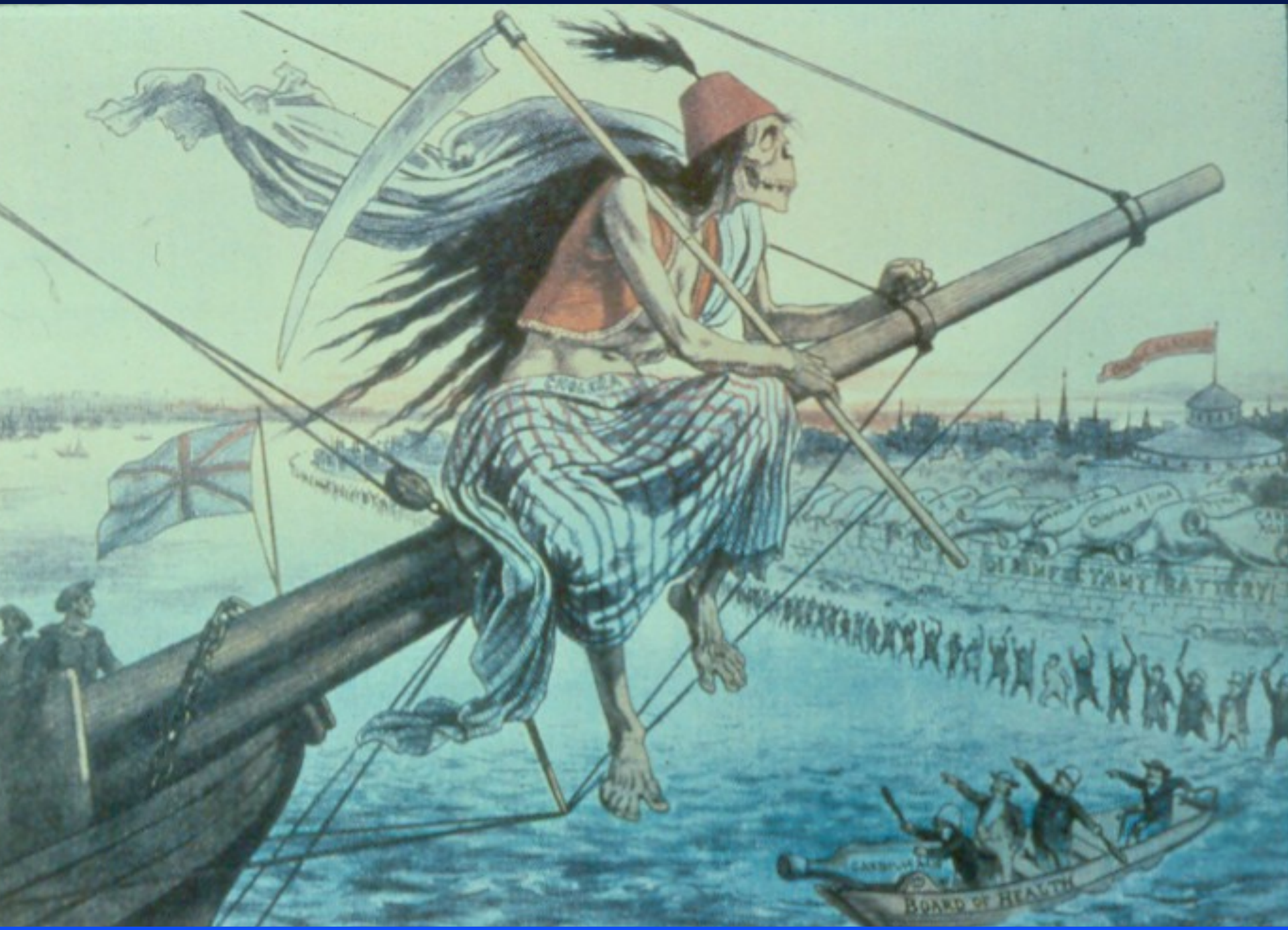
Campylobacteriosis
Campylobacter jejuni



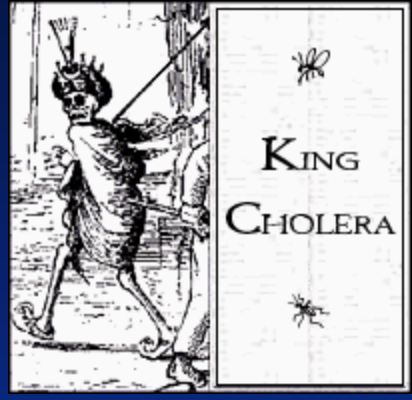
- **Labs:** fecal WBCs and RBCs; culture from stool on selective media
- **Rx:** azithromycin and quinolones bu increasing resistance
- **Pathogenesis:** spiral morphology, long polar flagella allow rapid motility and corkscrewing thru gut mucous.
- **Complications**: Guillain-Barre Syndrome is associated with prior *Campylobacter* infection in 30-40% of cases


BOARD OF HEALTH

Cholera
Vibrio cholerae

- **Most cases - <u>asymptomatic infection (~ 95%)</u>**
  - **Blood Group O more likely to develop severe disease**
  - **Achlorhydria increases risk Diarrhea - 500 to 1,000 ml/hr**
- **Fever - low-grade, if present (25%)**
- **Vomiting**
- **Tachycardia, hypotension and vascular collapse**
- **Dry tongue, oliguria, decreased skin turgor, sunken eyes, wrinkled fingers, raspy voice, acidosis, and Kussmaul breathing**
- **Infection to death from dehydration can occur in 24 hours**

Cholera
Treatment

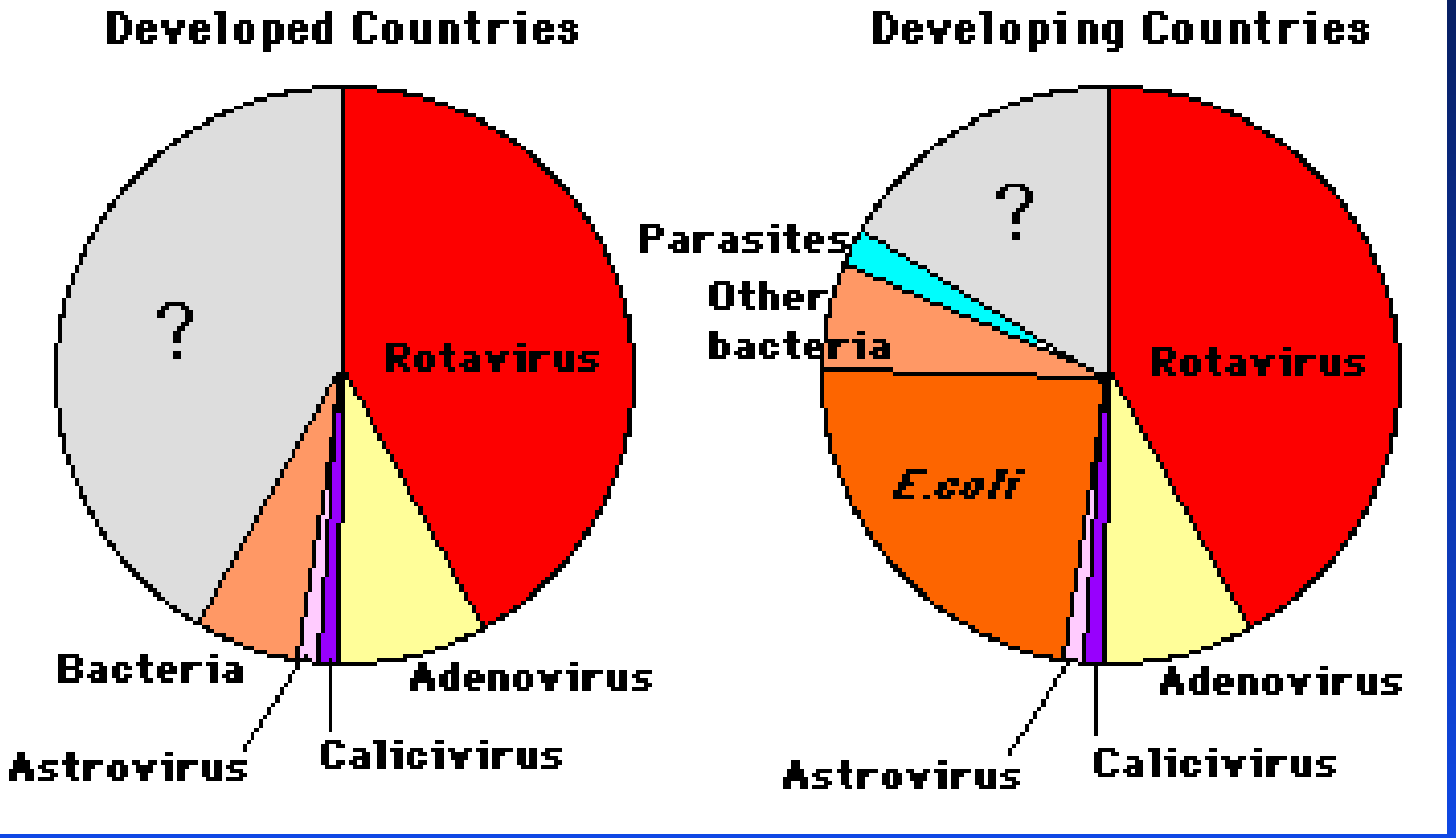


- **Primary therapy is rehydration**
  - **Cholera is the reason Oral Rehydration Solution (ORS) was developed**
  - **Attempt to replace fluid lost in diarrhea orally**
  - **Use IV fluids only if in shock or coma**
- **Tetracyclines have the longest track record**
  - **As little as one 300 mg dose of oral doxycycline will cure most cases of cholera**
  - **Some tetracycline resistant strains have developed**
- **Quinolones are first line in many areas**
- **TMP/SMX is recommended for pregnant women**

Table 3. **Etiologic Diagnoses within Selected Syndrome Groups, According to Travel Region.***

Syndrome and Cause	All Regions	Caribbean	Central America	South America	Sub-Saharan Africa	South Central Asia	Southeast Asia	Other or Multiple Regions†
	number of cases per 1000 patients with syndrome							
Systemic febrile illness (n=3907)								
Specific pathogen or cause reported‡	594	459	527	446	718	522	547	454
Malaria‡	352	65	133	133	622	139	130	234
Dengue‡	104	238	123	138	7	142	315	35
Mononucleosis (due to Epstein–Barr virus or cytomegalovirus)‡	32	70	69	79	10	17	32	63
Rickettsial infection‡	31	0	0	0	56	10	16	24
Salmonella typhi or *S. paratyphi* infection‡	29	22	25	17	7	141	26	24
No specific cause reported‡	406	541	473	554	282	478	453	546
Acute diarrhea (n=3859)								
Parasitic diarrhea‡	354	283	403	368	353	453	262	323
Giardiasis‡	173	132	136	158	177	286	118	132
Amebiasis‡	120	105	155	142	138	103	74	135
Presumptive parasitic cause‡	35	9	45	52	33	55	33	13
Bacterial diarrhea‡	268	260	190	253	250	294	369	227
Campylobacter infection‡	85	46	32	90	73	87	180	57
Shigella infection	41	37	26	41	46	61	26	34
Nontyphoidal salmonella infection‡	27	27	13	14	29	12	56	30
Presumptive bacterial cause	110	132	94	106	99	136	116	95
Viral diarrhea‡§	9	23	32	5	7	4	5	7
Unspecified acute diarrhea‡	385	457	377	376	397	289	393	451
Nondiarrheal gastrointestinal disorder (n=1421)								
Intestinal nematode infestation‡	239	278	273	256	307	202	344	141
Strongyloidiasis, simple intestinal‡	96	124	141	102	148	45	160	37
Ascaris infestation§	52	52	30	66	60	84	18	46
Gastritis or peptic ulcer disease‡	131	258	91	168	85	101	104	156
Helicobacter pylori status unknown	76	124	51	73	60	62	74	91
Positive for *H. pylori*‡§	47	103	40	80	22	28	25	60
Acute hepatitis‡	115	62	91	102	76	214	61	144
Hemorrhoids or constipation‡	89	124	192	117	54	84	74	84

Not all travel diarrhea is bacterial



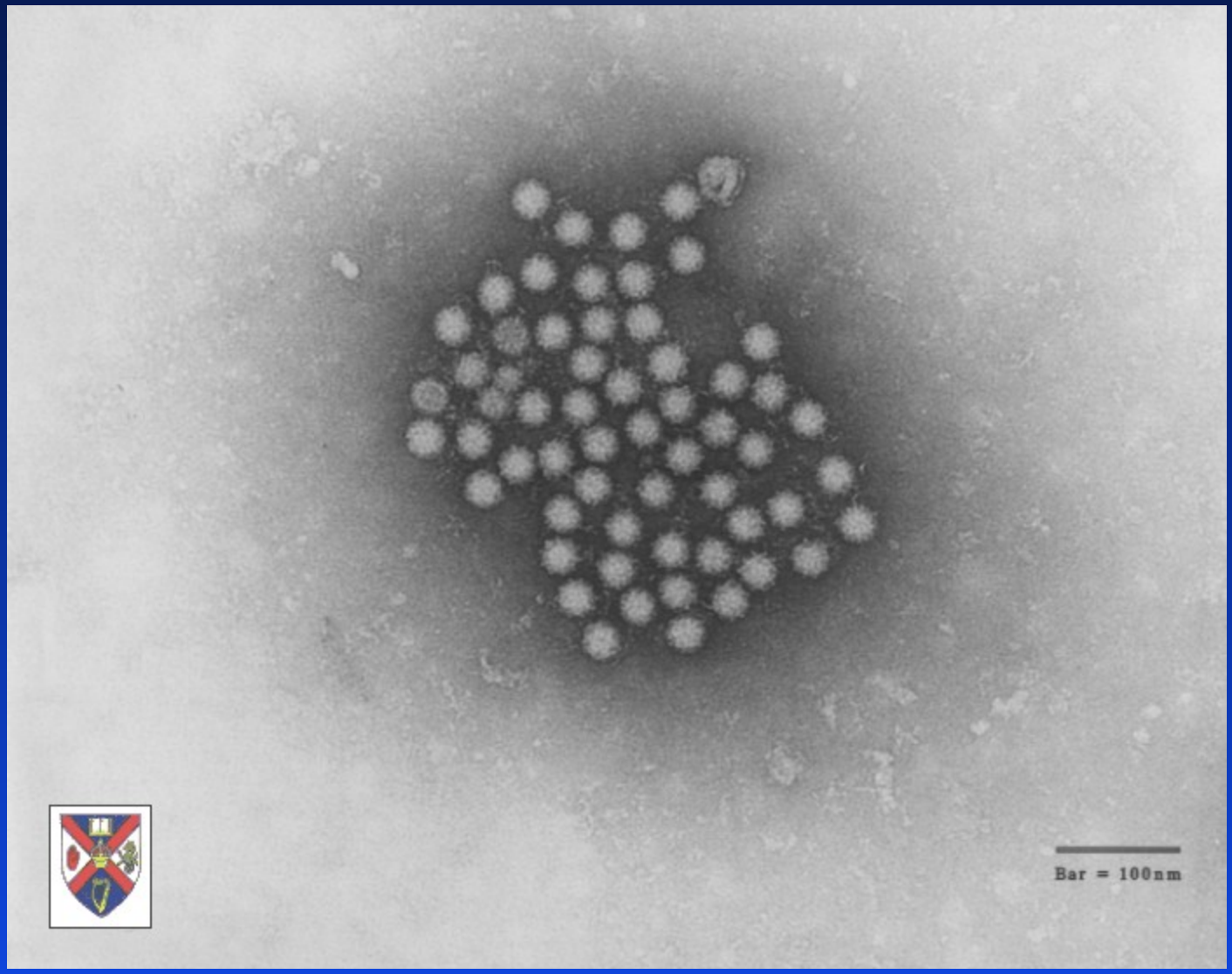
Etiology of Diarrhea in Children < 24 months old

Norwalk Virus: Desert Storm

A Study of 883 USMC & Navy, Dec 90 - May 91

Symptoms	Norwalk ELISA
vomiting only	23.5%
vomiting & diarrhea	12%
diarrhea only	6.5%
neither	3%

JID 1993;167:986-7. Note: 61% had GI sx, 9.4% had 4-fold rise of ELISA sero



Caliciviruses

Cruise Ship Associated Diarrhea

- Norwalk-like Viruses (Norovirus)
- Frequently spread via fomites
- Hand washing is most important
- Increased number of children on cruise ships probably plays a role

“Noro” Virus Diarrhea

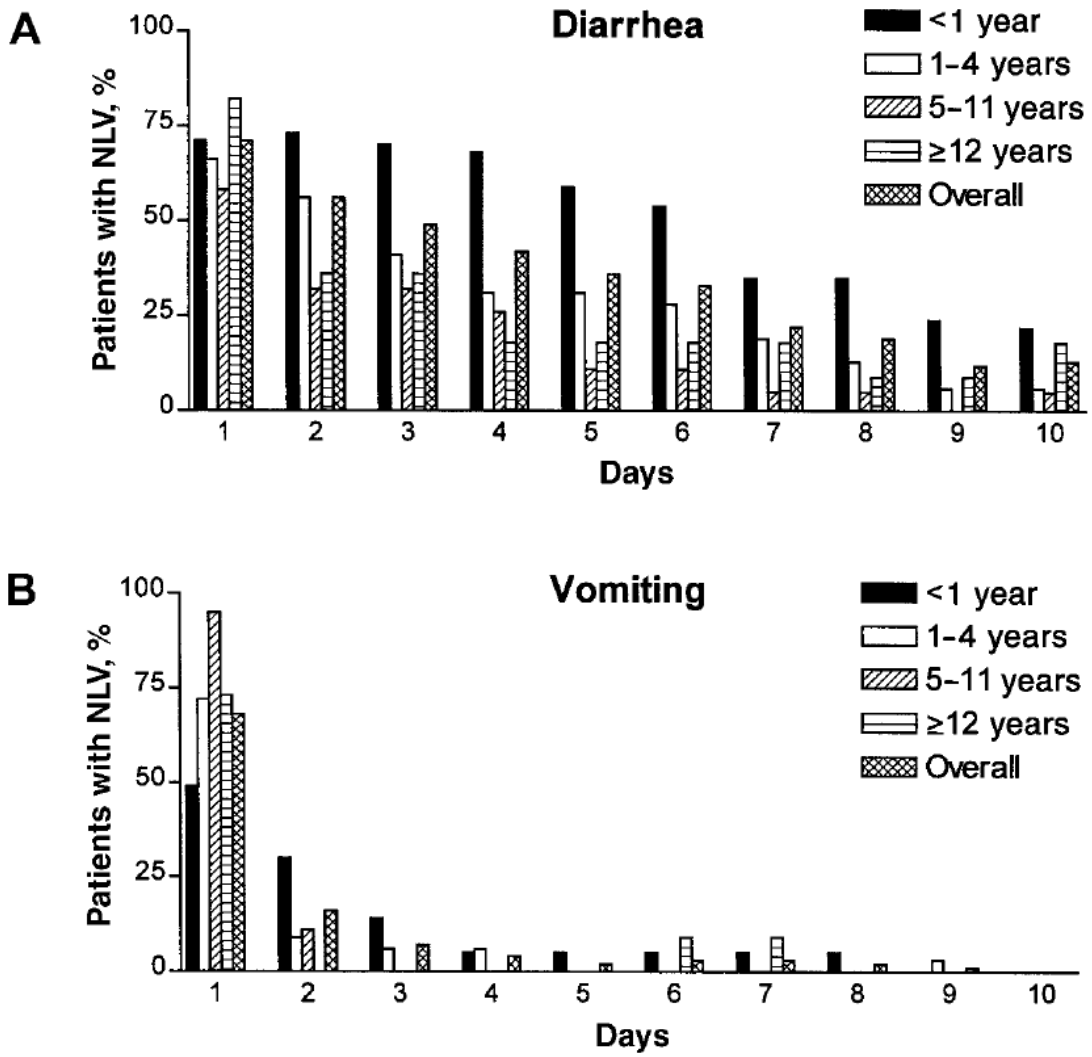


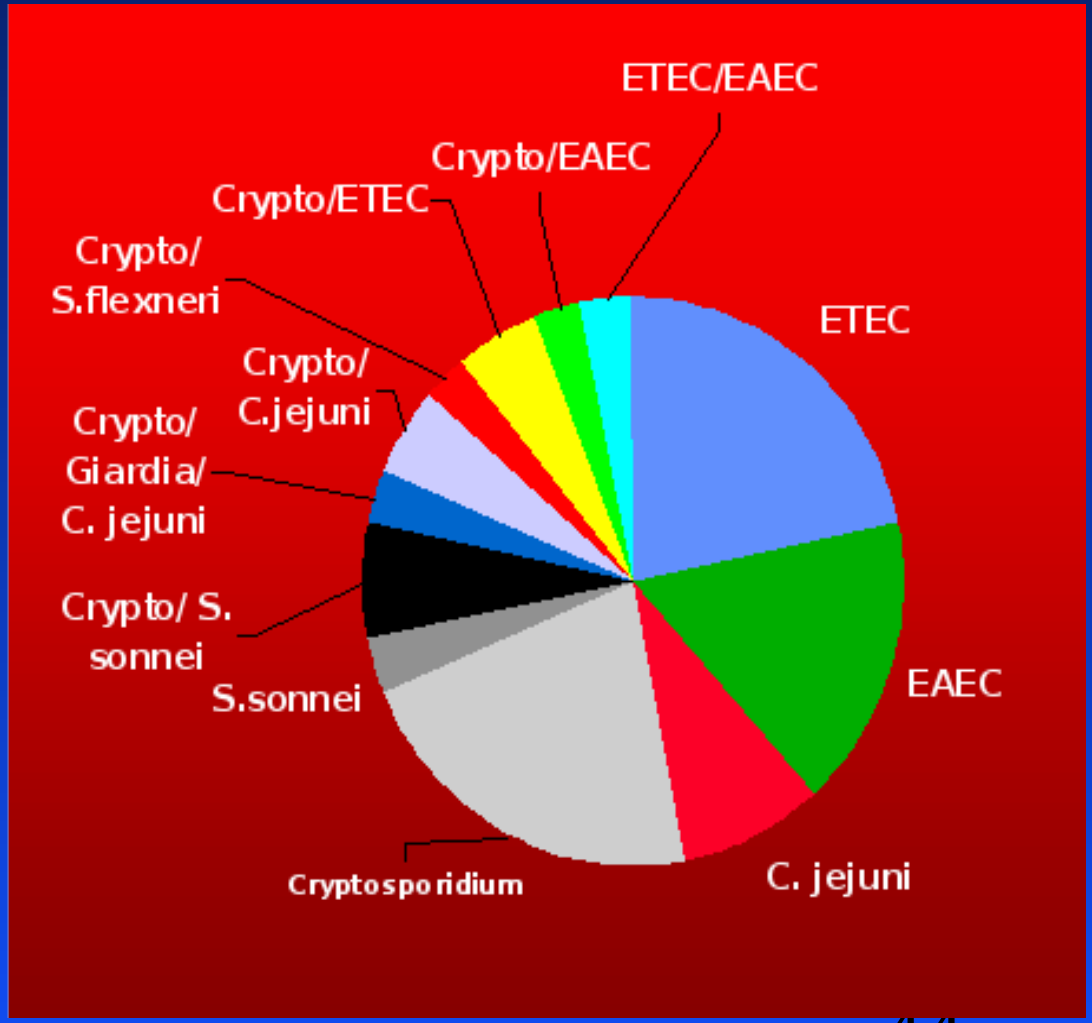
Figure 2. Proportion of Norwalk-like virus (NLV) cases associated with diarrhea *(A)* or vomiting *(B)* in patients aged <1, 1–4, 5–11, and ≥12 years

Rockx et al CID 2002; 35:246–53

Enteropathogens in Cusco, Perú

Parasites may be quite common

- 78 travelers from developed countries visiting Cusco, Perú
- 62% of those with diarrhea had a pathogen isolated
  - Multiple pathogens were found in 29%
  - Cryptosporidium was the single most common pathogen found in 48% (of positive specimens)



Cabada et al. Abstracts ASTM&H, 2004. Miami, Florida

Food “Poisoning”

Staph aureus

- Pre-formed heat-stable toxin

- Dx: vomiting and diarrhea 1 - 4 hours after ingestion

Clostridium perfringens

- Nausea, no vomiting, abdominal cramps, and watery diarrhea 8 - 16 hours after ingestion

Bacillus cereus

- Mimics staph, and can also mimic *C. perfringens*

- Associated with ingestion of re-cooked rice

Diagnosis and Therapy

Drug-Resistant Traveler's Diarrhea?

615 Bacterial Isolates in US Students with TD Summering in Guadalajara

	1988	1997
Ampicillin	38%	58%
Doxycycline	31%	69%
Furazolidone	21%	69%
Trimethoprim	3.4%	71%
Fluoroquinolones	3.4%	71%

DuPont et al Abstract 204 at 36th IDSA in *CID* Vol 27 No 4, Oct 98

Traveler's Diarrhea
Empiric Treatment in Adults

Severity	Antibiotic	Antimotility Agent
Mild (1 – 2 loose stools without fever or blood)	Not indicated	Observe or loperamide 2 mg after each loose stool or bismuth subsalicylate 2 qid
Moderate (<3 BMs without fever or blood)	Quinolones x 3d OR Azithromycin 500mg qd x3; Consider 1 dose therapy if sx resolve in 1 d	Loperamide or bismuth
Moderate to Severe (>3 BMs with fever and/or cramping)	Quinolones or Azithromycin as above, would avoid single dose therapy	Loperamide or bismuth
Severe (>6 BMs with fever and/or heme, tenesmus)	Quinolones or Azithromycin, may consider therapy for five days	Avoid unless close observation

Use of quinolones or azithromycin should be guided by area of travel. SE Asia should use azithro as first line. Levo-,gati- or gemifloxacin probably better than ciprofloxacin.

Rifaximin 200 mg tid x 3d can be substituted if bacterial diarrhea in area is almost exclusively *E. coli*

Traveler's Diarrhea in Children
Empiric Treatment in Children

- **Controversial due to increased risk of HUS in *EHEC* cases treated with antibiotics**
- **TMP/SMX is generally recommended, but high levels of resistance in the tropics (and increasing worldwide)**
- **If child did not respond to TMP/SMX, consider using cefixime or azithromycin.**
  - **Ceftriaxone can also be used IM or IV once daily**
- **Quinolones are not approved in < 16 yo, but contraindications are mainly from animal studies.**
- **Rifaximin also not approved in children but no reason to suspect it would not be effective or is dangerous**

Azithromycin for Diarrhea?

Single dose 1000 mg azithro vs 500 mg levo

Table 2. Microbiologic outcome after treatment with azithromycin or levofloxacin in US students who acquired travelers' diarrhea in Guadalajara, Mexico.

Pathogen	Azithromycin group (n = 105)		Levofloxacin group (n = 106)	
	No. of subjects with pathogen identified	Microbiologic cure, % of subjects	No. of subjects with pathogen identified	Microbiologic cure, % of subjects
ETEC alone	55	55	57	61
Shigella species	1	100	3	100
Salmonella species	1	100	2	100
Shigella species and ETEC	5	80	8	100
Salmonella species and ETEC	0	0	1	100
Any bacterial pathogen	62	58	71	69

NOTE. Denominators used to calculate percentages of subjects with microbiologic cure may differ from overall no. of subjects in whom pathogens were identified, because posttreatment samples were not always available. ETEC, enterotoxigenic *Escherichia coli*.

Azithromycin (105 subjects) vs. levofloxacin (106 subjects) for treatment of travelers' diarrhea (percentage remaining with diarrhea after initiation of therapy). Study performed in Guadalajara, Mexico

Adachi et al. Clin Infect Dis 2003; 37:1165-71

Pre Travel Antibiotics for Diarrhea

Is there a role for true prophylaxis?

- **Controversial**
- **Extremely high risk with short term, mission essential orders could consider:**
  - **Quinolones - avoid**
  - **Azithromycin - avoid**
  - **Bismuth – reasonable but side effects**
  - **Rifaximin – reasonable but expensive**
- **Risk of side effects may be substantial**
- **False sense of assurance → higher risk behavior**
- **Does not prevent viral, protozoal or helminthic infections**
  - **may increase likelihood of *Salmonella* infections**

Other PreTravel Recs to Decrease TD

- **Warn against unnecessary use of agents that decrease gastric acidity**
  - **The first line of defense against infection is gastric acidity**
  - **May decrease the infective dose 10-1000 fold**
- **Encourage frequent use of alcohol based handwashing agents like *Purell.***
- **Discuss water purification with trekkers or small group deployed.**

What Happens to all the Meds Dispensed?

Table. Use of Ciprofloxacin by Travelers (N = 70)

Measure Taken	Number	% of All Filled Prescriptions
Used all of the ciprofloxacin for:		
Travelers' diarrhea	2	2.9
Sore throat, fever	1	1.4
Used part of the ciprofloxacin for:*		
Travelers' diarrhea	5	7.1
Gas, bloating, or upset stomach	2	
Did not use any ciprofloxacin, but:		
Stored unused pills	40	57.1
Disposed of pills	13	18.6
Donated pills	2	
Unknown	2	
Other	3	4.3
Gave to a friend	1	
Gave to dog	1	
Lost	1	

* Of these 7 patients, 6 stored and 1 disposed of the remaining pills.

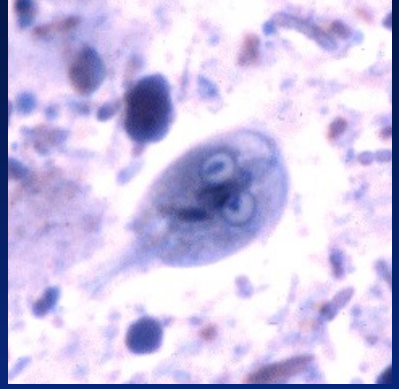
Day LJ - *Am J Med* - 15-JUN-2003; 114(9): 771-2

Work up for Diarrhea

- **Depends on the setting**
  - **Deployed with access to some lab:**
    - **Worthwhile to get stool cx and sens for initial cases to help define what pathogens are present and which therapy to use**
  - **Deployed with no lab but massive outbreak:**
    - **Collect stool in 3-5 cases and attempt to get sent to local lab or back to CONUS for w/u**
    - **Acute and convalescent serology may make dx**
  - **In CONUS with lab capability:**
    - **Typically viral, may not need antibx at all, if sporadic and mild dz, would not w/u**
    - **If large outbreak, worthwhile to check stools and possibly serology to determine etiology for future cases**

Post-Travel Diarrhea
Chronic

- **Diarrhea continuing for two weeks or longer usually presents after return from travel.**
- **Consider possible protozoal etiologies as more likely in this group:**
  - ***Giardia lamblia* is the most common.**
  - ***Entamoeba histolytica***
  - ***Cryptosporidium parvum***
  - ***Isospora belli***
  - ***Cyclospora cayetanensis***
- **Need fresh stool examined with conventional and modified acid fast staining.**
  - **May need repeated exams (three pick up > 90%).**
  - **May end up treating presumptively.**

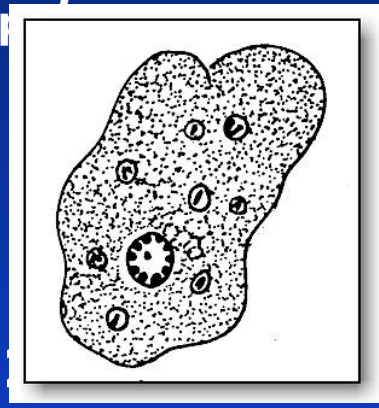


Giardiasis

- **The most prevalent enteric parasite in the US and Canada**
  - **~4% of 300,000 stool specimens**
- **In the developing world one of the 1st infections in infants**
  - **Peak prevalence rates 15-20% in children <10 yo.**
- **Generally water borne and probably carried by many animals**
- **Consider in all patients with prolonged diarrhea, especially if associated with malabsorption or weight loss.**
- **Dx with a stool EIA (more sens. than microscopy, esp. if inexperienced)**
- **Treat with metronidazole 250mg tid x 5 days or tinidazole 2.0 g x1.**
  - **Albendazole is alternative for metronidazole tolerant strains**
  - **Furazolidone 100 mg qid x 7d (available as suspension but $$$)**
  - **Nitazoxanide 500 mg po q 12 h x 3d (newly available in US)**

Amebiasis
Entamoeba histolytica

- ***E. histolytica* - very prevalent in Mexico, India, Africa, Central and S. America**
  - **morphologically indistinguishable but commensal, *E. dispar* causes far more infxns but is not associated with symp**



- **Routes of transmission:**
  - **Contaminated food and water**
  - **Direct fecal-oral contamination**

- **Symptomatic dz in 80-98% and invasive dz in**
  1. **Dysentery with small vol, bloody stools and fecal leuks**
  2. **Colitis with ulcerations of the mucosa and flask-shaped abscesses**
  3. **Formation of a fibrotic mass in the intestinal wall – ameboma**
  4. **Hematogenous spread of trophs to R lobe of the liver, brain, pericardium and lung**
  - **Chronic amoebic colitis is indistinguishable from inflammatory bowel dz**
    - **Use of steroids in these patients may lead to toxic megacolon and perforations**

Okhuysen CID 2001;33:110-4

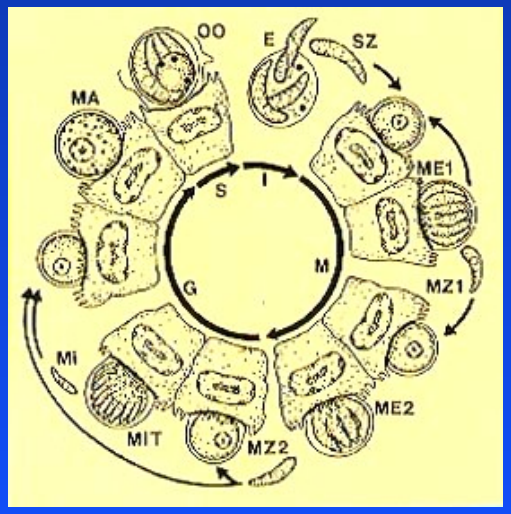
Amebiasis

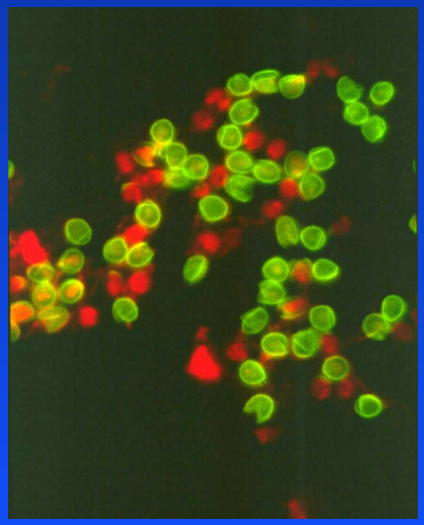
Entamoeba histolytic

- **Diagnosis**
  - **Fresh stool examination with Trichrome stain or PAS stain of colon bx**
  - **Fecal Ag studies using ELISA are needed to distinguish from *E. dispar***
- **Treatment**
  - **Metronidazole 750 tid x 10 d**
  - **Tinidazole 1.0 g bid x 3 d**
  - **Above work in tissue but are not luminal agents and must be followed by paromomycin 500 mg po tid x 7 d.**
  - **Nitazoxanide probably effective but not considered superior to metronidazole.**

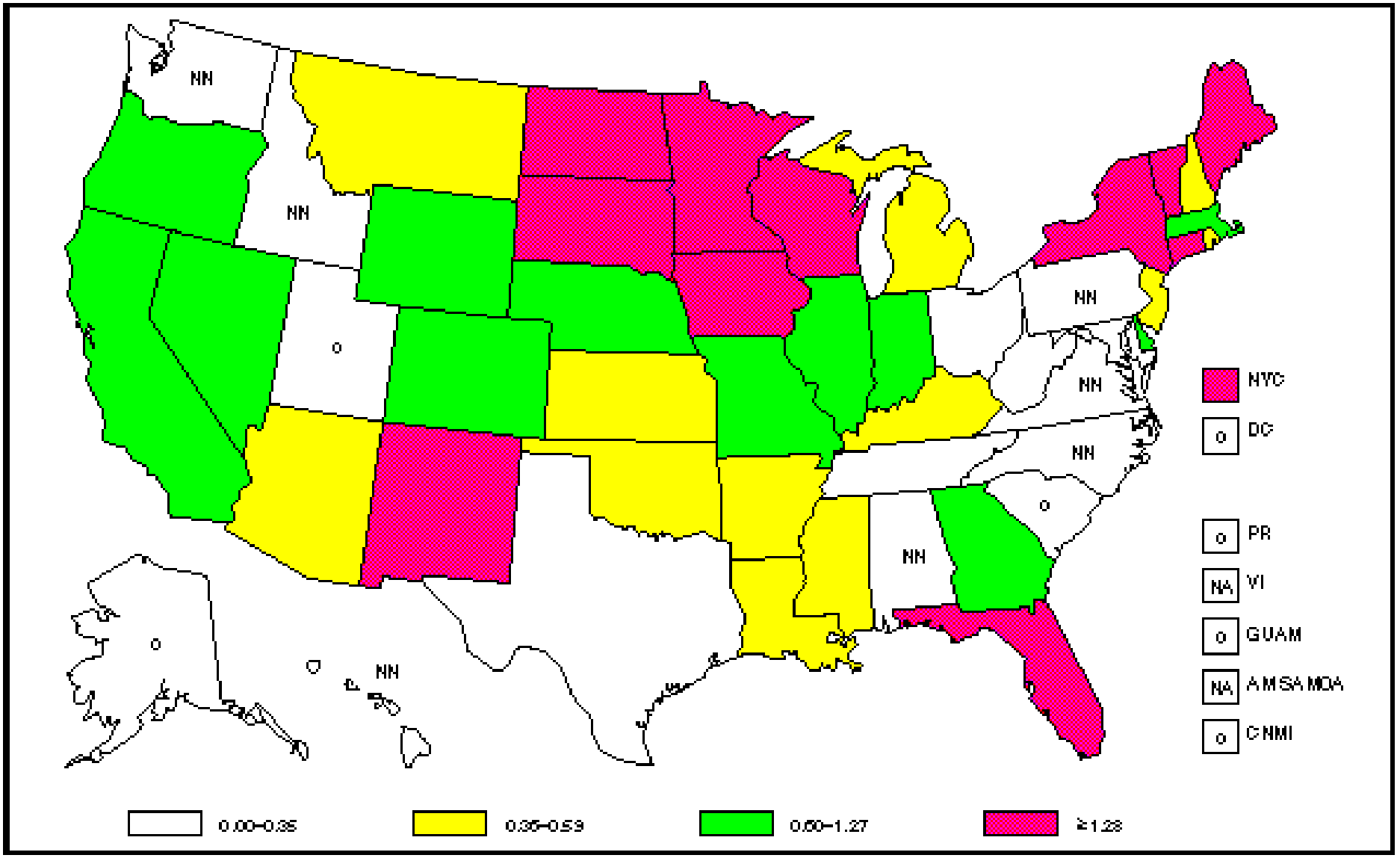
Cryptosporidiosis
Cryptosporidium hominis and *C. parvum*

- Protozoan pathogen of the small bowel increasingly recognized worldwide.
- 30-50% of US population with Ab
- 60-85% of developing countries pop. have Ab
- Often associated with water contaminated by cattle feces
  - Primarily infects neonatal animals
  - ~64 quadrillion cysts from US cattle annually



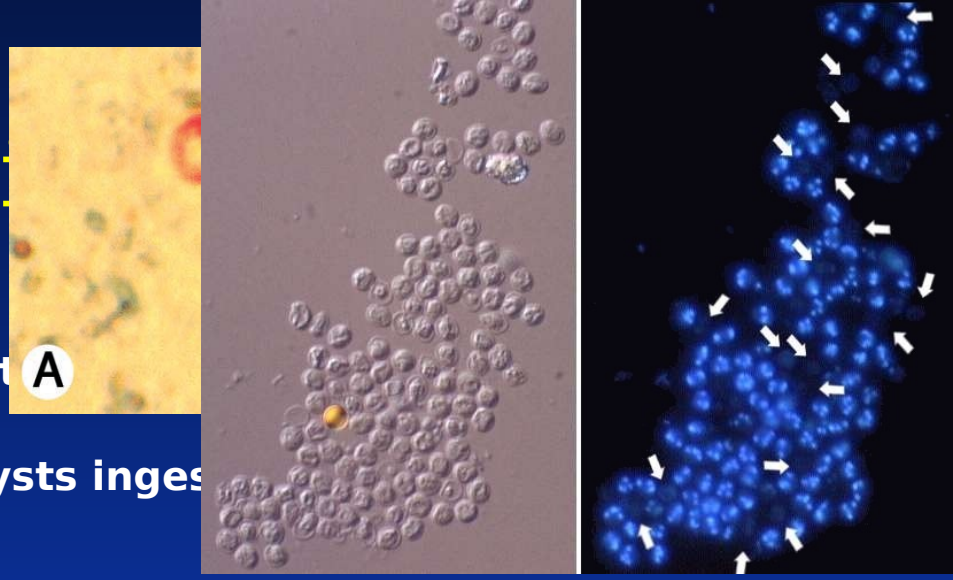


CRYPTOSPORIDIOSIS — reported cases per 100,000 population, United States and territories, 1997



Surveillance data from 1997 suggest that infection with cryptosporidium is geographically widespread. The highest reported rates were primarily in the north central and northeastern states. As in 1995 and 1996, cases primarily were reported in the late summer among children and adolescents aged <16 years.

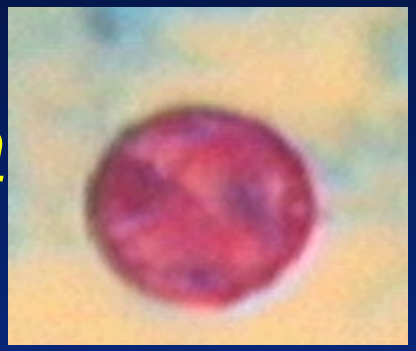
Cryptosporidiosis



- Rapid incubation, ~3 days post ingest
- Highly infectious with as few as 10 cysts inges
- Resistant to chlorine
- Self limited dz in immunocompetent, usually 5-7 days
  - Profuse watery diarrhea
  - Fatigue, malaise
  - Low grade fever
  - Nausea and vomiting in <20%
- Neonates, elderly and immunocompromised may have chronic diarrhea
- Diagnosis with modified acid fast stain or, more commonly stool EIA
- No therapy indicated (or very effective) in immunocompetent
  - In immunosuppressed with chronic diarrhea may try combination of azithromycin and paromomycin
  - Nitazoxanide 500 mg bid appears to be first effective drug (for chronic cases)

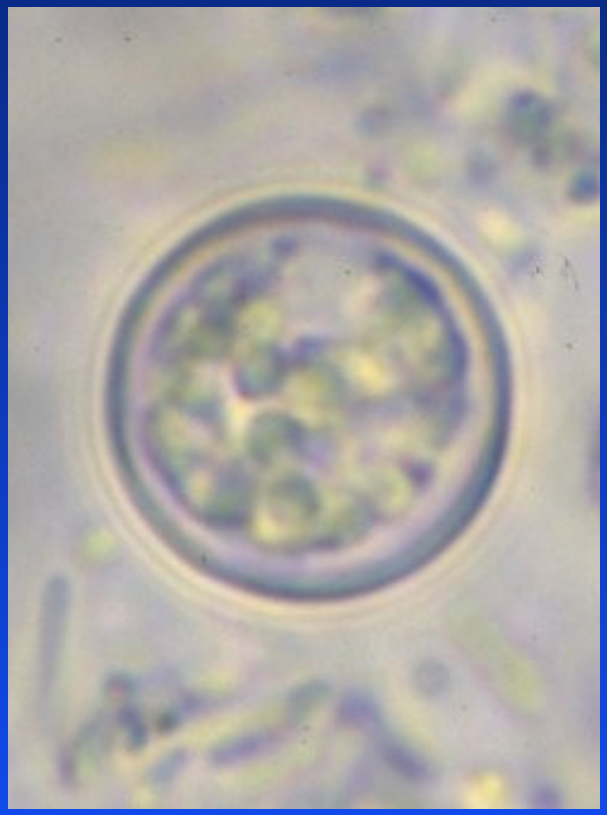
Leav et al. Clin Infect Dis 2003; 36:903–8

Cyclospora cayetanen



Acid fast stain oocyst

- Increasingly recognized as a cause of chronic diarrhea in travelers
- Associated with US foodborne outbreaks (raspberries & lettuce)
- Small bowel pathogen with sx similar to Giardia
- Waxing and waning course
  - diarrhea, nausea, anorexia, fatigue, malaise and weight loss
- Rx: TMP/SMX for 1 week.



Sporulated oocyst

Chronic Diarrhea

Helminths

- **Uncommon in most short term travelers**
  - **more common in those who return after months to years in the developing world**
- ***Ascaris, Strongyloides*, *Trichuris, Necator* and *Ancyclostoma* (hookworm) are the most common**
- **Light infections are typically asx after pulmonary phase has passed**
- **Heavy infestations are more likely to be symptomatic and are easier to dx.**
- **If scant number of eggs/larva then think about other undx orgs**
  - **ie. *Giardia, Entamoeba, Cryptosporidium***

Diarrhea in Travelers or Deployed

Work Up

Initial W/U

- Fresh stool sample
  - Not refrigerated overnight
- Fecal leukocytes
- Fecal occult blood
- Fecal lactoferrin

After initial W/U

- Culture and sensitivity
- EIA for Giardia and Cryptosporidium
- Stool microscopy for O&P (up to 3x)
  - If not examined fresh then fix immediately
  - Trichrome
  - Modified AFB

Water Disinfection for International and Wilderness Travelers

- **Heat is still the best way to inactivate all organisms in water**
- **Time consuming**
- **Fuel needed**
- **May disclose location if operational**

Organism	Lethal temperature and time
Giardia species	55°C[a] for 5 min 50°C for 10 min (95% inactivation) 60°C for 10 min (98% inactivation) 70°C for 10 min (100% inactivation)
Cryptosporidium species	64°C within 2 min 72°C heated up over 1 min
E. coli, and *Salmonella*, *Shigella*, and *Campylobacter* species	65°C[b] for 3 min
Vibrio cholerae	60°C for 10 min 100°C for 10 s
E. coli	60°C for 5 min 70°C for 1 min
Enteric viruses	56°C–60°C for 20–40 min <1 min at ⩾70°C[c]
Hepatitis A virus	98°C for 1 min 85°C for 1 min

Backer. CID; 2002; 34:355-64

Table 3. Susceptibility of microorganisms to filtration, by size.

Organism	Approximate size, μm	Maximum recommended filter rating, μm
Virus	0.03	NA[a]
Escherichia coli	0.5 × 3–8	0.2–0.4
Campylobacter species	0.2–0.4 × 1.5–3.5	0.2–0.4
Vibrio cholerae	0.5 × 1.5–3.0	0.2–0.4
Cryptosporidium oocyst	2–6	1
Giardia cyst	6–10 × 8–15	3–5
Entamoeba histolytica cyst	5–30	3–5
Nematode egg	30–40 × 50–80	20
Schistosome cercariae	50 × 100	Coffee filter or fine cloth
Dracunculus larvae	20 × 500	Coffee filter or fine cloth

[a] Not applicable to most portable filters; only reverse-osmosis membranes exclude viruses by virtue of pore size.

Table 4. Recommended contact time for specified halogen concentration, according to water temperature.

Halogen concentration	Contact time, min		
	At 5°C	At 15°C	At 25°C
2 ppm	240	180	60
4 ppm	180	60	45
8 ppm	60	30	15

NOTE. Contact times are extended from the usual recommendations to account for (1) uncertainty about the presence of residual halogen and (2) the time required to kill *Giardia* cysts in very cold water.

Halogen type, organism	Concentration, mg/L[a]	Time, min	Temperature, °C	Disinfection constant, Ct
Chlorine				
Escherichia coli	0.1	0.16	5	0.016
Campylobacter species	0.3	0.5	25	0.15
20 enteric viruses	0.5	60	2	30
Hepatitis A virus	0.5	5	5	2.5[b]
Entamoeba histolytica cysts	3.5	10	25	35
Giardia cyst	2.5	60	5	150
Cryptosporidium oocyst	10	720	20	1440
Schistosome cercariae	1.0	30	28	30
Iodine				
E. coli	1.3	1	2–5	1.3
E. histolytica cyst	3.5	10	25	35
	6.0	5	25	30
Poliovirus 1	1.25	39	25	49
Coxsackie virus	0.5	30	5	15
Giardia cyst	4	15	30	60[c]
	4	120	5	480[c]

NOTE. Most experiments use a 2–3-log (99%–99.9%) reduction as the end point.

[a] Residual concentration of active chlorine disinfectant compounds.

[b] End point of 4-log reduction.

[c] A 100% rate of killing organisms; viability tested only at 15, 30, 45, 60, and 120 min.

Table 6. Dose of halogen for field-water disinfection.

Method of disinfection	Amount of halogen administered (no. of drops[a])			
	For 4 ppm	For 5 ppm	For 8 ppm	For 10 ppm
Iodination added to 1 L or qt of water				
Iodine tablets (tetraglycine hydroperiodide; e.g., EDWGT, Potable Aqua, and Globaline)[b]	1/2 tablet	—	1 tablet	—
2% Iodine solution (tincture)	0.2 mL (5)	—	0.4 mL (10)	—
10% Povidone-iodine solution	0.35 mL (8)	—	0.70 mL (16)	—
Saturated solution (iodine crystals in water; e.g., Polar Pure[c])	13 mL	—	26 mL	—
Chlorination added to 1 L or 1 qt of water				
Household bleach 5%; sodium hypochlorite	—	0.1 mL (2)	—	0.2 mL (4)
Chlorine tablets (sodium dichloroisocyanurate [e.g., AquaClear[d]])	—	—	—	1 tablet
Chlorine plus flocculating agent (e.g., AquaCure, AquaPure, or Chlor-Floc[e])	—	—	1 tablet	—

NOTE. EDWGT, emergency drinking water germicidal tablet.

[a] Measured with a dropper (1 drop = 0.05 mL) or a small syringe.
[b] Manufactured by Coghlan's Ltd., Wisconsin Pharmacal, and Van Ben Industries, respectively.
[c] Manufactured by Polar Equipment.
[d] Manufactured by Gal Pharmaceuticals.
[e] Manufactured by Safesport, World Resources, and Control Chemical, respectively.

Table 8. Choice of filtration method for types of water from various sources.

Primary concern and filtration method used	"Pristine" water in the wilderness	Tap water in developing country	Water in a developed or developing country	
			Clear surface[a]	Cloudy
Primary concern				
Giardia species, enteric bacteria	X	—	—	—
Bacteria, *Giardia* species, small numbers of viruses	—	X	—	—
All enteric pathogens, including *Cryptosporidium* species	—	—	X	—
Unpleasant taste plus microorganisms	—	—	—	X
Method used				
Heat	X	X	X	—
Filtration[b]	X	X	—	—
Halogen	X	X	—	—
Coagulation-flocculation followed by a second step (heat, filtration, or halogen)	—	—	—	X
Filtration plus halogen[c] (done in either order)	—	—	X	—

[a] Found near areas of human and animal habitation; includes agricultural runoff (from cattle grazing) or sewage treatment effluent (from upstream villages or towns).

[b] Filtration alone is adequate for eliminating *Cryptosporidium* species introduced by cattle grazing in high-quality wilderness.

[c] May include iodine resin filters (for considerations, see the "Iodine resins" subsection of the "Halogens" section of the text).

Diarrhea Prevention
Closing Points

- **Education prior to travel**
  - **food, water, hygiene issues for patients**
  - **knowledge of diarrhea epidemiology for the health provider**
- **Treatment**
  - **Proper antibiotic for primary pathogens**
  - **Antimotility agents in conjunction**
- **Work up of cases**
  - **Handling of specimens**

Case 1

- **You are the medical officer with a MEU deployed to Operation Cobra Gold in Thailand**
- **It is ~day 12 in country, you have had ~1-2 cases/day of mild diarrhea thru sick call for the first 10 days**
- **You noticed that this has increased to 6-8 cases/day for the last two days and some of the patients are returning with continued sx.**
- **Today the Corpsman gets you while you're eating breakfast to tell you that there are at least 20 Marines in the sick call line with diarrhea**

- **As you wade through the morning sick call you find the following:**
  - **Most patients c/o crampy abdominal pain associated with nausea and loose stools**
  - **2/21 had fever, the remainder were afebrile**
  - **The two febrile patients also had heme positive (but not grossly bloody) stool**

- **What pathogens should you be considering?**

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  - ***Campylobacter* sp.**
  - **ETEC**
  - ***Shigella* sp.**
  - ***Salmonella* sp.**

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  - ***Campylobacter* sp.**
  - **ETEC**
  - ***Shigella* sp.**
  - ***Salmonella* sp.**
  - **Viruses such as Noro**
  - ***Protozoa such as***
    - ***Cryptosporidium***
    - ***Giardia***

- **Considering the prevalence of quinolone resistant *Campylobacter* sp. before you deployed, you have a large supply of azithromycin, all in the form of "Z-Paks"**

- **How do you instruct the Marines to take the azithromycin?**

- **Considering the prevalence of quinolone resistant *Campylobacter* sp. before you deployed, you have a large supply of azithromycin, all in the form of "Z-Paks"**

- **How do you instruct the Marines to take the azithromycin?**
  - **500 mg qd for 3 days**
  - **1000 mg as a single dose**

- **It is two days later:**
  - **yesterday and today you have also had ~20-25 Marines with diarrhea, including some of those who are returning and have received therapy for two days**

- **What should you consider?**

- **What potential diarrheal pathogens have resistance to azithromycin?**

- **Viruses**
  - **Norwalk and Norwalk like caliciviruses**
  - **Rotavirus**
  - **Adenovirus**
  - **Numerous others**
- **Macrolide resistant strains of bacteria**
- **Protozoal pathogens**
  - ***Giardia***
  - ***Cryptosporidia***
  - ***Entamoeba***
  - ***Cyclospora***

- **You decide to investigate possible sources of infection, where should you look?**

- **Food**
  - **All from approved US sources or is some local?**
  - **Are there opportunities for Marines to eat local food?**
  - ***Hand washing before meals***
- **Water**
  - **Same questions as above**
- **Fomites**
  - **Diaper changing?**
  - ***Hand washing after using latrines***

Case 2

- **You are a flight surgeon at Incirlik AFB in Turkey, the clinic has full microscopy and culture capabilities**
- **Sick call has ~ 3-5 cases of acute diarrhea daily, the standard therapy is levofloxacin 500 mg qd x 3 d**
- **You are seeing a 26 yo ♀ Sgt who is on her third day of antibx and continues to have fever and blood tinged stools**

- **She has not had stool studies performed previously, you send off fecal leuks and culture.**

- **What do you do while awaiting results?**

- **She has not had stool studies performed previously, you send off fecal leuks and culture.**

- **What do you do while awaiting results?**
  - **More complete physical exam DOCUMENTED**
  - **Assess hydration status with tilts**
  - **Rehydrate orally or IV as appropriate**
  - **Ask about adherence with levofloxacin**

- **She is somewhat dehydrated and you decide to give her two liters of fluid while awaiting labs.**
- **Sheets of fecal leuks are seen and there are many RBCs**
- **Should you change her antibx?**
  - **If so, to what?**

- She is somewhat dehydrated and you decide to give her two liters of fluid while awaiting labs.

- Sheets of fecal leuks are seen and there are many RBCs

- **Should you change her antibx?**
  - **If so, to what? Any other recs?**

  - **Consider trial of azithromycin**
  - **Consider stool exam for protozoa**

Case 3

- **You are evaluating a 34 yo ♂ Major who returned 2 months ago from a 3- week trip to Brazil.**
- **He has complained of diarrhea for nearly 5 weeks**
- **What do you want to ask him about his illness?**

- **You are evaluating a 34 yo ♂ Major who returned 2 months ago from a 3- week trip to Brazil.**
- **He has complained of diarrhea for nearly 5 weeks**
- **What do you want to ask him about his illness?**
  - **Frequency of bowel movements?**
  - **Presence of blood or mucous?**
  - **Presence of abdominal cramping/pain?**
  - **How much weight loss (if any)?**
  - **Presence of gas (above and below)?**
  - **Other associated symptoms such as anorexia, fever, etc?**
  - **Others with same symptoms?**
  - **Any other treatments, antibx**

- **He has watery, blood tinged stools, 3-4x per day and has lost ~10-15 lbs.**
- **His appetite is diminished and he has frequent nausea and vague abdominal pain.**
- **He has completed two 5 day courses of levofloxacin, each time feeling slightly improved while on antibiotics**

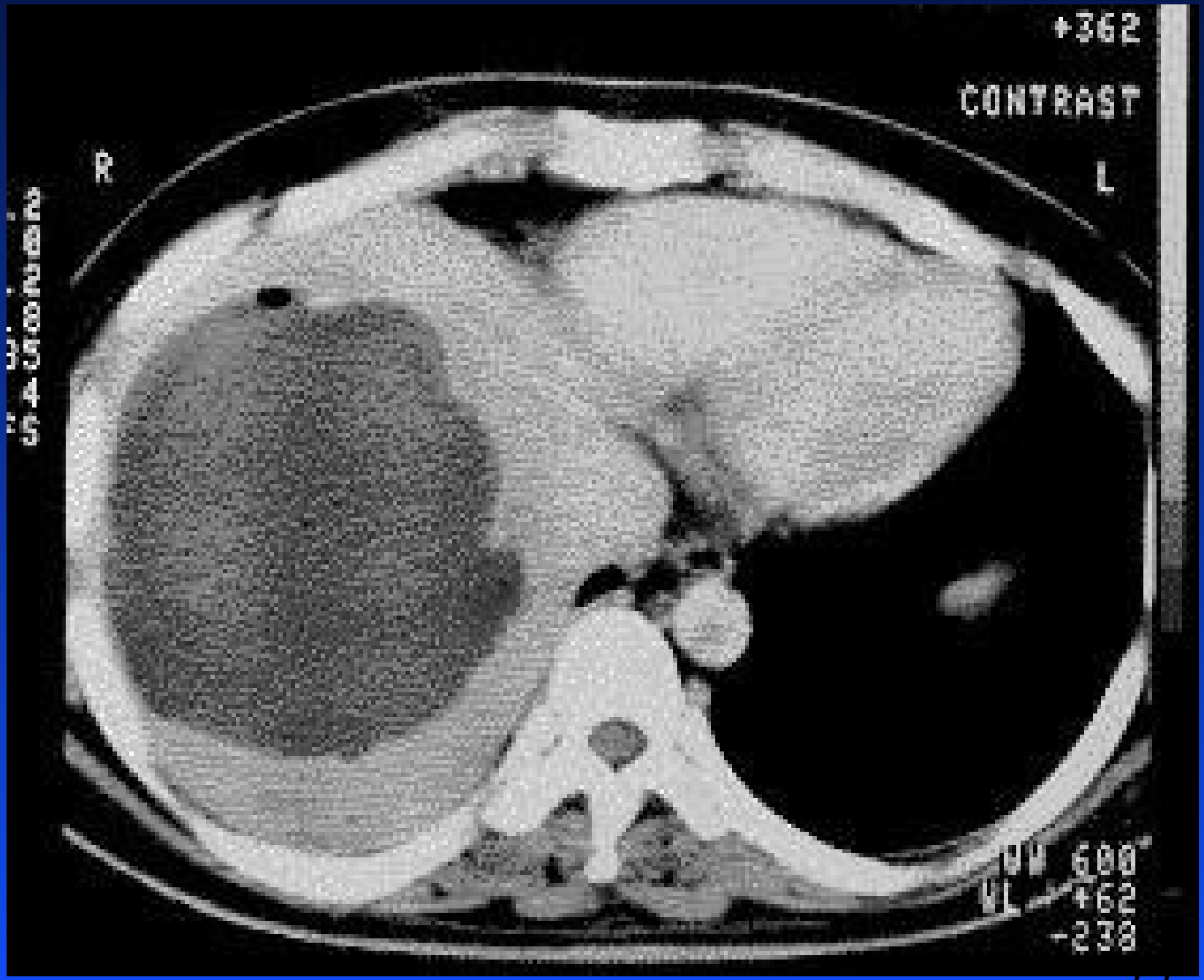
- **What do you order to evaluate his sx?**

- **What do you order to evaluate his sx?**
  - **Fecal Studies**
    - **WBCs, RBCs**
    - **Culture (routine bacterial)**
    - **Giardia, Cryptosporidium stool Ag ELISA**
    - **Consider protozoal studies**
      - **Trichrome stain, wet prep (varies with lab)**
      - **Modified acid fast**
  - **Blood Studies**
    - **CBC with diff**
    - **Amoebic serology**
    - **Blood cultures**

- **He has now been checking his temperature and has fever 2-3x/daily to as high as 102.3°F**
- **There are no fecal leuks but there are numerous RBCs**
- **His WBC is 13.2 with 78S 4B 16L 2E**
- **How does the above change your differential?**

- **Ova and parasites x3 are negative**
- **Amoebic serology is strongly positive**
- **Any other labs you should consider?**

- Ova and parasites x3 are negative
- Amoebic serology is strongly positive
- Any other labs you should consider?
  - Imaging with Ultrasound or CT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Case 4

- **MWR has arranged for a 3 day cruise on a Carnival ship from Miami.**
- **Numerous families with children from your command have decided to take the cruise**
- **The ship has just returned from a Caribbean cruise and there is widespread media attention to the >75 cases of diarrhea that occurred.**
- **Your CO calls and wants to know if she should have MWR cancel the trip**

- **What is the most likely etiologic agent(s) of the diarrhea on the ship?**

- **What is the most likely etiologic agent(s) of the diarrhea on the ship?**
  - **Norwalk-like viruses i.e. caliciviruses; “winter vomiting illness”**
- **The tour company tells MWR that if the group cancels they will lose 75% of the cost of the trip**

- **The CO decides the group should be permitted to go. She wants you to have a “town meeting” where you explain her decision.**

- **What recs do you make?**

You actually did get this from the doorknob

- Fomites, fomites, fomites
- Water and food can be implicated
  - Especially buffets where people contaminate the food that was initially clean
- Frequent handwashing, especially before meals
  - Use of alcohol based waterless lotions such as Purell® should be encouraged
- Children may be an important amplifying factor

Case 5

- **You are seeing a 32 yo ACDU ♀ Tech Sgt who complains of occasional mild, crampy abdominal pain and watery stools for ~3-4 weeks.**
  - **BMs are ~3-5 per day and have not been associated with blood or mucous**
  - **She has lost ~8lbs from her baseline 132lbs**
  - **She is most annoyed by waking up once or twice per night to have a BM**
- **What questions do you want to ask her?**

- **She is stationed at Travis AFB (where you are seeing her now), she has not traveled outside the US with the exception of 4 days in Mexico ~5 years ago.**
- **She did spend a month with her family at their lake house in Kentucky before arriving at Travis ~ 4 weeks ago**
- **What do you recommend?**

a. Counsel her that she is likely experiencing IBS due to stress with a new job at a new duty station

b. Recommend loperamide prn and tell her to come back if sx persist for 2 more weeks

c. Check stool culture and fecal leuks

d. Check stool for O&P

e. Recommend upper and lower endoscopy with biopsies

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- **Stool cultures are negative**
- **Military health center calls to tell you that on her reenlistment PE her WBC was 9.9 with 22% eos**
- **What are you thinking of now?**

- **Stool cultures are negative**
- **Military health center calls to tell you that on her reenlistment PE her WBC was 9.9 with 22% eos**
- **What are you thinking of now?**
  - ***Giardia lamblia***
  - ***Entamoeba histolytica* (amebiasis)**
  - ***Cryptosporidium parvum***
  - ***Cyclospora cayetanensis***
  - ***Necator americanus* (hookworm)**
  - ***Strongyloides stercoralis***
  - ***Enterobius vermicularis* (pinworm)**
- **Can you get these things in the US?!**

Hookworm egg in stool

martin@nmrcd.med.navy.mil
COM 001 511 562-3848
FAX 011 511 561-3042

US NMRCD-Perú
American Embassy, Unit 3800
APO AA 34031-3800

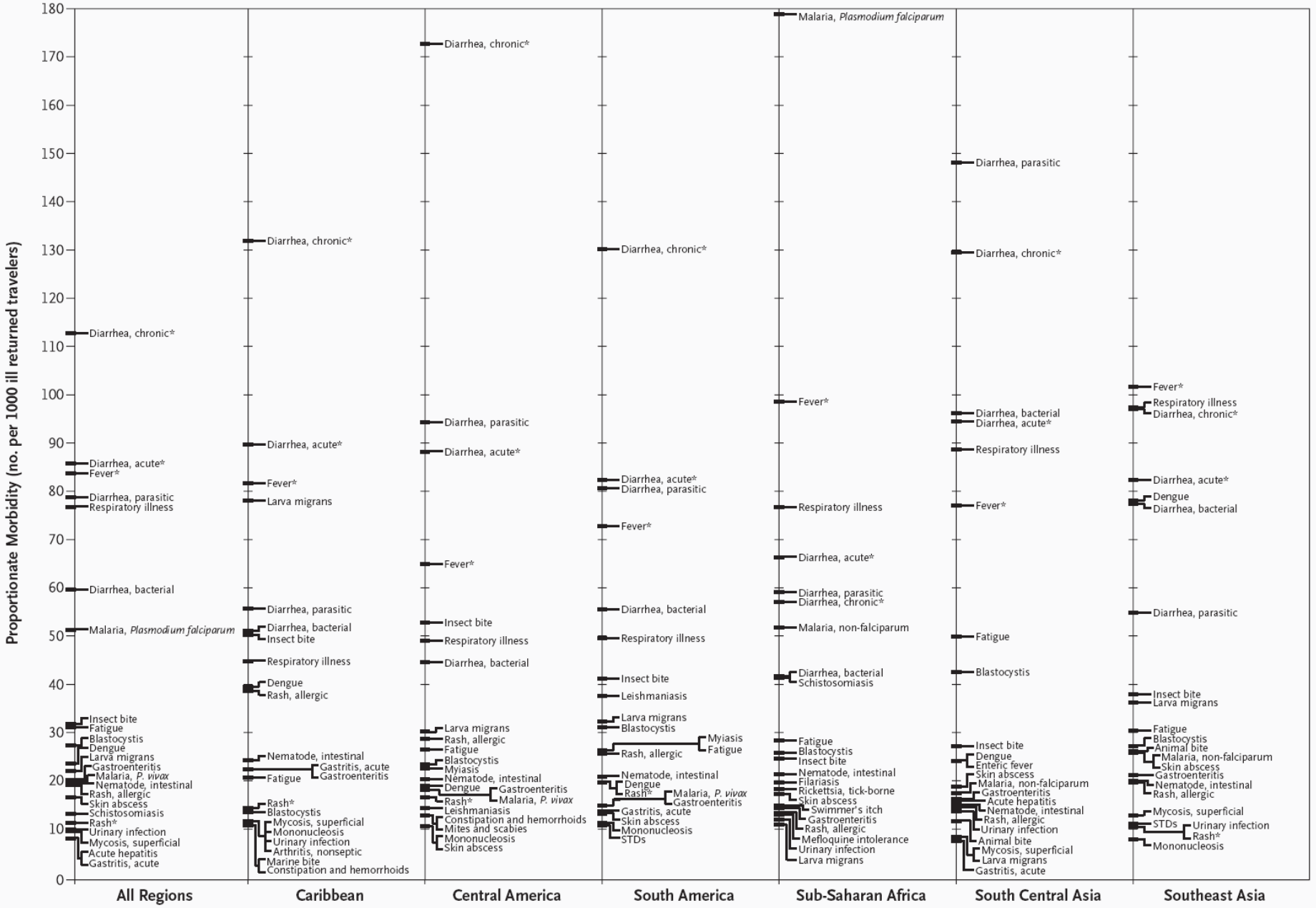

Figure 2. Proportionate Morbidity among Ill Travelers Returning from the Developing World, According to Region of Travel.

The proportions are shown, not incidence rates, of each of the top 22 specific diagnoses for all ill returned travelers within each of the regions. STD denotes sexually transmitted disease. Asterisks indicate syndromic diagnoses for which specific etiologic diagnoses could not be assigned.